## **Remarks**

In the Office Action dated October 1, 2003, claims 17-25, 28, 30, 32 and 33, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the following remarks. Claims 17-25, 28, 30, 32 and 33 remain in this application and claims 1-16, 26-27, 29 and 31 have been canceled.

In the only remaining rejection, claims 17-25, 28, 30, and 32-33 were rejected under 35 USC §112, first paragraph. Applicants respectfully point out that at the priority date of the present application, it was known that the 7 cysteine region was of great importance for all members of the TGF-ß superfamily. This is clearly explained in the specification of the present application for example on page 4, lines 8 and 9 and page 12, lines 6-8. The 7 cysteine region determines the 3-dimensional folding of BMPs and is decisive for receptor binding. Attached to this response is data in the form of an unsigned declaration which shows that a fragment of MP52 starting with the first of the 7 conserved cysteines is active. A signed copy of this declaration will be filled shortly. The attached *in vitro* data, in the form of the ALP-assay, shows that a MP52 fragment with the 7 cysteines can bind to receptors and shows activity. Additionally, the data shows that MP52 has been crystallized and shows the expected folding with the cysteine knot.

The N-terminal region of MP52, however, cannot be fixed which indicates that amino acids which are before the 7 cysteine region are not important but as the attached data shows, longer fragments containing the decisive 7 cysteine

region should always be active. The attached data indicates that a fragment starting with the first cysteine (amino acid 400) would have the correct 3-dimensional folding (which is necessary for activity) regardless of the N-terminal amino acids, as discussed in the office action.

Applicants point out that Example 2 of WO 97/04095 shows that longer fragments than the mature protein (propeptide + mature: amino acids 28-501, part of the propeptide + mature: amino acids 48-501) are also active in the APL-assay.

Applicants also point out US Patent Nos. 6,426,332 and 6,281,195, which were granted a couple of years ago. These patents show that broad claims on osteogenic proteins such as BMPs or GDFs as well as amino acid variants thereof have been found acceptable and enabled. In the broadly granted claims of these applications, MP52 (GDF-5) as well as amino acid variants thereof are encompassed even though the examples of these patents are restricted to OP1 only and do not provide disclosure for all osteogenic proteins and/or fragments in the form of examples. According to column 9, line 52 of US 6,426,332, within the osteogenic proteins comprised by claim 1, there are also preferably those, which only contain a C-terminal sequence consisting of 102-106 amino acids, i.e. the 7 conserved cysteine region, and which only have a 70% homology to OP1, BMP-2 or related proteins. Under "Background of the Invention" this patent states that: "Members of this family encode secreted polypeptide chains sharing common structural features, including processing from a precursor 'pro form' to yield a mature polypeptide chain competent to dimerize and containing a carboxy

terminal active domain of approximately 97-106 amino acids." The shortest fragment, which is protected in the present application, is longer than the 97 amino acids recited in this patent. Applicants respectfully contend that these patents show that one skilled in the art would not have any difficulty determining which fragments have activity when the critical region has been determined as in the present invention.

A patent application, which discusses MP52 in combination with other particular BMPs, is WO 96/39170, which was published one month after the priority date of the present application. This application clearly describes that proteins, which belong to the subfamily of BMP-12 similar proteins, (MP52 belongs thereto), can be combined with other BMPs. This is understandable since different BMPs can act at different times when bone and cartilage is formed. Please see page 3 of WO 96/39170 and the disclosure at line 12 and line 21. Example 4 of WO 96/39170 shows a combination of BMP-13 with BMP-2 and also shows that BMP-2 and BMP-13 alone can have different properties. In view of this, applicants contend that contrary to statements made in the office action, there is no reason to believe that MP52 fragments in combination with another protein of the TGF-β family would not have cartilage or bone inducing activity as indicated in the present application.

In view of the attached declaration, the disclosure in the present application and the above discussion, applicants contend that all of the fragments recited in the present claims would be expected to have cartilage and/or bone inducing potential.

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Applicants respectfully submit that all of claims 17-25, 28, 30, 32 and 33 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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Enclosure: 132 declaration